amended as set forth herein. The Applicants do not intend to surrender the subject matter of the previously pending claims by making these amendments. The applicants will pursue the prosecution of the previously pending claims in another application, and ask that the amendments are made without prejudice.

Support for amended claims 1, 7, 22, and 25 can be found throughout the specification and in the originally filed dependant claims 4 and 5. Support for the newly added claims 32-35 can be found in the specification at page 16, lines 13-20. Claims 4 and 5 were amended for clarity, no new matter was added.

Response to Rejection Under 35 U.S.C. § 102(e)

Claims 1, 3-5, 7, 15, 16, 18-22, and 25-31 are rejected under 35 U.S.C. § 102(e) as being clearly anticipated by Walt *et al.* (U.S. Patent No. 6,023, 540). The Examiner asserts that Walt *et al.* anticipates the decoder binding ligand limitation, because Walt *et al.* discloses that "the optical response of the microspheres is changed as a result of binding of entity "64," for example a fluorescent dye, to the microspheres." Applicants respectfully traverse.

Walt *et al.* is directed to the preparation and use of fiber optic sensors with encoded microspheres. Walt *et al.* relies on a system of optical signature encoding of the biosensor with dyes and is silent with respect to identifier binding ligands and decoding binding ligands, wherein the identifier binding ligands are nucleic acids.

Claim 1 is directed to an array composition comprising a population of microspheres comprising at least 2 subpopulations. The first and second subpopulation comprise a first and second bioactive agent and a first and second identifier binding ligand. The first and second bioactive agents are proteins. The first and second

identifier binding ligands are nucleic acids.

Claim 7 is directed to a method of making a composition comprising providing a surface comprising individual sites on a substrate at a density of at least 100 sites per 1 mm^2. The method also comprises randomly distributing microspheres on the surface. The microspheres comprise at least 2 subpopulations. The first and second subpopulation comprise a first and second bioactive agent and a first and second identifier binding ligand. The first and second bioactive agents are proteins. The first and second identifier binding ligands are nucleic acids.

Claim 22 is directed to an array composition comprising a population of microspheres comprising at least 2 subpopulations. The first and second subpopulation comprise a first and second bioactive agent, a first and second identifier binding ligand, and a first and second decoder binding ligand. The first and second bioactive agents are proteins. The first and second identifier binding ligands are nucleic acids. The first and second decoder binding ligands are bound to the first and second identifier binding ligands, respectively.

Claim 25 is directed to a method of making a composition comprising forming a surface comprising individual sites on a substrate, randomly distributing microspheres on the surface, so that the sites contain microspheres, and binding a first and second decoder binding ligand to a first and second identifier binding ligand. The microspheres comprise at least a first and second subpopulation. The first and second subpopulation comprise a first and second bioactive agent and the first and second identifier binding ligand. The and second bioactive agents are proteins. The first and second identifier binding ligands are nucleic acids.

As the Examiner is aware, "[i]t is axiomatic that for prior art to anticipate under

§ 102 it has to meet every element of the claimed invention." *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986). The law is well established that in order to anticipate a claim, the prior art must disclose "each and every element"of the claimed invention. *SSIH Equipment S.A.v. U.S. Inc. Int'l. Trade Commission,* 218 USPQ 678, 688 (Fed. Cir. 1983). As stated by the Federal Circuit in *In re Bond,* 15 USPQ2d 1566, 1567 (Fed. Cir. 1990), "[f]or a prior art reference to anticipate in terms of 35 U.S.C. § 102, every element of the claimed invention must be identically shown in a single reference." See also *Glaverbel Societe Anonyme v. Northlake Marketing & Supply, Inc.*, 33 USPQ2d 1496 (Fed. Cir. 1995).

Again, claims 1 and 7 in this application are directed to an array composition and a method of making this array composition, respectively, that comprise random distribution of microspheres containing a bioactive agent and an identifier binding ligand onto a surface with discrete sites, wherein at least one of the bioactive agents is a protein and the identifier binding ligands are nucleic acids. Claims 22 and 25 are directed to a composition and a method of making this composition, respectively, that comprise randomly distribution of microspheres containing a bioactive agent, an identifier binding ligand and a decoder binding ligand onto a surface with discrete sites wherein at least one of the bioactive agents is a protein, and the identifier binding ligands are nucleic acids. Each of these independent claims recites that the microspheres contain a bioactive agent and an identifier binding ligand, wherein within at least one subpopulation of microspheres the bioactive agent is a protein and the identifier binding ligand is nucleic acid. However, Applicants note that Walt is silent with respect to teaching that microspheres include both bioactive agents that are proteins and identifier binding ligands that are nucleic acids.

Accordingly, Applicants submit that Walt *et al.* does not teach each element of claims 1, 3-5, 7, 15, 16, 18-22, and 25-31. Applicants respectfully request the Examiner to

withdraw this rejection.

Response to Rejection Under 35 U.S.C. § 102

Claims 1, 4, 5, 7, 18, 20, 30 and 31 are rejected under 35 U.S.C. § 102(b) and (e) as being clearly anticipated by Ekins *et al.* (U.S. Patent No.5,516,635). The Examiner notes, "the microspheres of Ekins *et al.* bind to the surface to form an array of microspheres on the surface." The Examiner suggests that Ekins *et al.* anticipates the claims because identifier binding ligands must be present on the microspheres , because binding cannot occur in a vacuum and thus random distribution of microspheres on a surface and the use of identifier binding ligands is taught. Applicants respectfully traverse.

Ekins *et al.* teaches a binding assay process for an analyte using a capture binding agent with binding sites specific for the analyte and microspheres that contain a developing binding material capable of binding with the bound analyte or with the binding sites on the capture binding agent either occupied by the bound analyte or the remaining unoccupied binding sites.

Claims 1 and 7 in this application are amended and are directed to an array composition and a method of making this array composition, respectively, that comprise random distribution of microspheres containing bioactive agents and identifier binding ligands onto a surface with discrete sites, wherein the bioactive agent and identifier binding ligand are a protein and nucleic acid, respectively.

As noted above, "for prior art to anticipate under § 102 it has to meet every element of the claimed invention." *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986).

Initially, Applicants note that claims 1 and 7 require that microspheres are mandomly distributed on the surface. Indeed, as disclosed in the specification as filed, p. 6, line 30-32, "the beads may be randomly distributed on the array, a fast and inexpensive process as compared to either the in situ synthesis or spotting techniques of the prior art." Thus, the present invention, in this important aspect, is distinct from prior art such as Ekins et al that requires a process to spot "binding entity" on a surface first. That is, the surface of Ekins does not contain beads that are randomly distributed. Rather, the beads associate with a site that is dictated by the developing binding material.

Furthermore, Ekins *et al.* does not teach or suggest identifier binding ligands at all. Ekins certainly does not teach or suggest an identifier binding ligand that is a nucleic acid. As noted at page 20, lines 9-14 in the specification, an identifier binding ligand is "meant a compound that will specifically bind a corresponding decoder binding ligand (DBL) to facilitate the elucidation of the identity of the bioactive agent attached to the bead. That is, the IBL and the corresponding DBL form a binding partner pair." However, that is not what Ekins does. Ekins does not have an identifier binding ligand because, the microspheres of Ekins contain a single class of antibodies and a flourescent label. The fluorescent label on Ekins is not an identifier binding ligand, because it will not bind a decoder binding ligand. The microspheres of Ekins comprise an antibody, but this is also not the same as an identifier binding ligand, as defined in the specification.

Accordingly, Applicants submit that Ekins et al fails to anticipate each element of the claims.

The Examiner also notes that "the remaining claim limitations directed to nucleic acid or protein binding agents are disclosed in Ekins *et al.*," and "Ekins *et al.* also cites

several types of markers or labels...[and discloses] solid supports, such as specifically described plastic walls of microtitre plates." However, Applicants respectfully submit that "the remaining claim limitations" are disclosed in claims 4, 5, 30, and 31 that are dependent on allowable independent claims.

Therefore, Ekins et al does not anticipate every element of claims 1, 2, 6, 7, and 22-25 of the present invention. Accordingly, the claims at issue are allowable under 35 U.S.C. § 102; Applicants respectfully request the Examiner to withdraw the rejection.

Response to Rejection under 35 U.S.C. § 103

Claims 1-7, 18, 20, and 22-31 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Ekins *et al.* (U.S. Patent No. 5,516,635), taken in view of Matthews *et al.* The Examiner suggests that Ekins describes the usage of enzyme markers or labels and detectable labels. The Examiner further notes Matthews is a review of such entities. The Examiner asserts that "such generic suggestion in Ekins is reasonably suggestion [sic] to utilize a review such as Mathews for labels and/or marker practice." Applicants respectfully traverse.

Ekins *et al.* teaches a binding assay process for an analyte using a capture binding agent with binding sites specific for the analyte and microspheres that contain a developing binding material capable of binding with the bound analyte or with the binding sites on the capture binding agent either occupied by the bound analyte or the remaining unoccupied binding sites.

Matthews *et al.* is a review that "describe[s] the various labels and strategies for DNA probe assays," at p.1, column 1, para. 1. Matthews *et al.* teaches a variety of DNA probe assays that utilize direct labeling of DNA probes with radioactive, fluorescent or

enzyme labels. This review also teaches indirect procedures in DNA probe assays including the usage of proteins that specifically interact with a nucleic acid duplex.

Claims 1, 7, 22, and 25 teach compositions and methods that utilize a surface comprising individual sites on a substrate at a density of at least 100 sites per 1 mm^2. The compositions and methods also comprises randomly distributing microspheres on the surface. The microspheres comprise at least 2 subpopulations. The first and second subpopulation comprise a first and second bioactive agent and a first and second identifier binding ligand. The and second bioactive agents are proteins. The first and second identifier binding ligands are nucleic acids.

Claims 2, 6, 23, and 24 teach compositions and methods that utilize a surface comprising individual sites on a substrate at a density of at least 100 sites per 1 mm^2. The compositions and method also comprises randomly distributing microspheres on the surface. The microspheres comprise at least 2 subpopulations. The first and second subpopulation comprise a first and second bioactive agent and a first and second identifier binding ligand, wherein bioactive agents do not comprise a label.

Applicants note that there are three requirements to establish a prima facie case of obviousness. These include that "there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations." (MPEP § 2143).

With regard to claims 1, 7, 22, and 25, Applicants submit that there is no motivation to combine the references. Ekins does not suggest employing the binding of

a decoder binding ligand to an identifier binding ligand in a microsphere-based assay system. Neither does Matthews *et al.* provide any motivation to employ the described DNA probes including the enzyme-substrate systems as an identifier binding ligand or a decoder binding ligand in a microsphere-based system.

Furthermore, Applicants submit that the cited references fail to teach or suggest all the claim limitations, because neither Ekins nor Matthews teaches or suggests bioactive agents and identifier binding ligands, wherein they are proteins and nucleic acids, respectively. As described above, independent claims 1 and 6 in this application are amended and are directed to an array composition and a method of making this array composition, respectively, that comprise random distribution of microspheres containing bioactive agents and identifier binding ligands onto a surface with discrete sites, wherein the bioactive agent and identifier binding ligand are a protein and nucleic acid, respectively.

With regard to independent claims 2, 6, 23, and 24, Applicants submit that Ekins *et al.* in light of Matthews *et al.* does not provide motivation for the combination of the references to employ an array composition and a method of making such a composition by random distribution of microspheres onto a surface with discrete sites, wherein bioactive agents do not comprise labels, because the binding assays of Ekins in light of Matthews utilize labeled microspheres. Ekins relies on a form of specific interaction between a developing binding material and a capture binding agent or an analyte.

The present claims require no labels; however, as the Examiner has noted, Ekins in fact does utilize labels and Matthews is specifically drawn to labels. Moreover, Applicants draw the Examiner's attention to the specification of the present invention on page 27, lines 5-13. The paragraph states, in part, that "labels include enzymes." Thus, Ekins *et al.* in light of Matthews *et al.* does not lead to the compositions and

methods in claims 2, 7, and 24, because they claim that the microspheres "do not comprise a label."

Accordingly, Applicants submit that a prima facie case of obviousness has not been made. Applicants respectfully request the Examiner to withdraw the rejection.

CONCLUSION

Applicants submit that the claims as amended are in form for immediate allowance and the Examiner is respectfully requested to early notification to that effect.

The Examiner is invited to contact the undersigned at (415) 781-1989 if any issues may be resolved in that manner.

Respectfully submitted,

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APPENDIX A: CURRENTLY PENDING CLAIMS

1. (Amended) An array composition comprising:

a) a substrate with a surface comprising discrete sites at a density of at least 100 sites per 1 mm^2; and

b) a population of microspheres comprising at least a first and a second subpopulation, wherein said first and said second subpopulations comprise:

i) a first and second bioactive agent, respectively wherein said first and second bioactive agents are a protein; and

ii) a first and second identifier binding ligand, respectively, wherein said first and second bioactive agents are a protein;

wherein said microspheres are randomly distributed on said surface.

2. An array composition comprising:

a) a substrate with a surface comprising discrete sites at a density of at least 100 sites per 1 mm^2; and

b) a population of microspheres comprising at least a first and a second subpopulation, wherein said first and second subpopulations comprise a first and second bioactive agent, respectively, and do not comprise a label, wherein said microspheres are randomly distributed on said surface.

3. A composition according to claim 1, 2 or 17, further comprising at least one decoder binding ligand.

4. (Amended) A composition according to claim 2, 17, or 23, wherein said bioactive agents are nucleic acids.

5. (Amended) A composition according to claim 2, 17, or 23, wherein said bioactive

agents are proteins.

6. A method of making a composition comprising:

a) providing a surface comprising individual sites on a substrate at a density of at least 100 sites per 1 mm^2;

b) randomly distributing microspheres on said surface such that said individual sites contain microspheres, wherein said microspheres comprise at least a first and a second subpopulation, wherein said first and second subpopulations comprise a first and a second bioactive agent, respectively, and do not comprise a label.

7. (Amended) A method of making a composition comprising:

a) providing a surface comprising individual sites on a substrate at a density of at least 100 sites per 1 mm^2;

b) randomly distributing microspheres on said surface such that said individual sites contain microspheres, wherein said microspheres comprise at least a first and a second subpopulation, wherein said first and second subpopulations comprise:

i) a first and second bioactive agent, respectively, wherein said first or second bioactive agent is a protein; and

ii) a first and a second identifier binding ligand, wherein said first and second identifier binding ligands are nucleic acids.

15. The composition according to claim 1, 2, 17, 22 or 23, wherein said discrete sites are wells.

16. The method according to claim 6, 7, 24 or 25, wherein said discrete sites are wells.

17. An array composition comprising:

a) a substrate with a surface comprising discrete sites, wherein said substrate is a fiber optic bundle; and

b) a population of microspheres comprising at least a first and a second subpopulation, wherein each subpopulation comprises a bioactive agent and does not comprise a label, wherein said microspheres are randomly distributed on said surface.

18. A composition according to claim 1, 2, 22 or 23, wherein said substrate is selected from the group consisting of glass and plastic.

19. A composition according to claim 1, 2, 22 or 23, wherein said substrate is a fiber optic bundle.

20. A method according to claim 6, 7, 24 or 25, wherein said substrate is selected from the group consisting of glass or plastic.

21. A method according to claim 6, 7, 24 or 25 wherein said substrate is a fiber optic bundle.

22. (Amended) An array composition comprising:

a) a substrate with a surface comprising discrete sites; and

b) a population of microspheres comprising at least a first and a second subpopulation, wherein said first and second subpopulations comprise:

i) a first and a second bioactive agent, respectively, wherein said bioactive agent is a protein;

ii) a first and second identifier binding ligand, respectively, wherein said identifier binding ligand is a nucleic acid; and

iii) a first and a second decoder binding ligand, bound to said first and second identifier binding ligands, respectively;

wherein said microspheres are randomly distributed on said surface.

23. An array composition comprising:

a) a substrate with a surface comprising discrete sites; and

b) a population of microspheres comprising:

i) at least a first and a second subpopulation, wherein said first and second subpopulations comprise a first and a second bioactive agent, respectively, and do not comprise a label; and

ii) a first and a second decoder binding ligand bound to said first and second bioactive agent, respectively;

wherein said microspheres are randomly distributed on said surface.

24. A method of making a composition comprising:

a) providing a surface comprising individual sites on a substrate;

b) randomly distributing microspheres on said surface such that said individual sites contain microspheres, wherein said microspheres comprise at least a first and a second subpopulation comprising a first and second bioactive agent, respectively; and

c) binding a first and second decoder binding ligand to said first and second bioactive agent, respectively;

wherein said microspheres do not comprise a label.

25. (Amended) A method of making a composition comprising:

a) forming a surface comprising individual sites on a substrate;

b) randomly distributing microspheres on said surface such that said individual sites contain microspheres, wherein said microspheres comprise at least a first

and a second subpopulations, wherein said first and second subpopulations comprise:

i) a first and second bioactive agent, respectively, wherein said bioactive agent is a protein; and

ii) a first and second identifier binding ligand, respectively, wherein said identifier binding ligand is a nucleic acid; and

c) binding a first and second decoder binding ligand to said first and second identifier binding ligand.

26. A method according to claim 6 further comprising:

c) binding a first and second decoder binding ligand to said first and second bioactive agent.

27. A method according to claim 7 further comprising:

c) binding a first and second decoder binding ligand to said first and second identifier binding ligand.

28. A method according to claim 24, 25, 26 or 27, wherein at least said first decoder binding ligand comprises a label.

29. A composition according to claim 3, wherein said at least one decoder binding ligand comprises a label.

30. A composition according to claim 1, wherein said first bioactive agent is said first identifier binding ligand.

31. A method according to claim 7, wherein said first bioactive agent is said first identifier binding ligand.

32. (New) A composition according to claims 1, 4, or 22, wherein said nucleic acid is double-stranded.

33. (New)A composition according to claim 1, 4, or 22, wherein said nucleic acid is single-stranded.

34. (New)A method according to claim 7 or 25, wherein said nucleic acid is double-stranded.

35. (New)A method according to claim 7 or 25, wherein said nucleic acid is single-stranded.

36. (New) A method according to claim 7, wherein said first and second bioactive agents are proteins.

APPENDIX B: VERSION TO SHOW CHANGES MADE

1. An array composition comprising:

a) a substrate with a surface comprising discrete sites at a density of at least 100 sites per 1 mm^2; and

b) a population of microspheres comprising at least a first and a second subpopulation, wherein said first and said second subpopulations comprise:

i) a first and second bioactive agent, respectively, wherein said first and second bioactive agents are a protein; and

ii) a first and second identifier binding ligand, respectively, wherein said first and second identifier binding ligands are nucleic acids;

wherein said microspheres are randomly distributed on said surface.

2. An array composition comprising:

a) a substrate with a surface comprising discrete sites at a density of at least 100 sites per 1 mm^2; and

b) a population of microspheres comprising at least a first and a second subpopulation, wherein said first and second subpopulations comprise a first and second bioactive agent, respectively, and do not comprise a label, wherein said microspheres are randomly distributed on said surface.

3. A composition according to claim 1, 2 or 17, further comprising at least one decoder binding ligand.

4. A composition according to claim [1,]2, 17, [22] or 23, wherein said bioactive agents are nucleic acids.

5. A composition according to claim [1,] 2, 17, [22] or 23, wherein said bioactive agents are proteins.

6. A method of making a composition comprising:

a) providing a surface comprising individual sites on a substrate at a density of at least 100 sites per 1 mm^2;

b) randomly distributing microspheres on said surface such that said individual sites contain microspheres, wherein said microspheres comprise at least a first and a second subpopulation, wherein said first and second subpopulations comprise a first and a second bioactive agent, respectively, and do not comprise a label.

7. A method of making a composition comprising:

a) providing a surface comprising individual sites on a substrate at a density of at least 100 sites per 1 mm^2;

b) randomly distributing microspheres on said surface such that said individual sites contain microspheres, wherein said microspheres comprise at least a first and a second subpopulation, wherein said first and second subpopulations comprise:

i) a first and second bioactive agent, respectively, wherein said first or second bioactive agent is a protein; and

ii) a first and a second identifier binding ligand, wherein said first and second identifier binding ligands are nucleic acids.

15. The composition according to claim 1, 2, 17, 22 or 23, wherein said discrete sites are wells.

16. The method according to claim 6, 7, 24 or 25, wherein said discrete sites are wells.

17. An array composition comprising:

a) a substrate with a surface comprising discrete sites, wherein said substrate is a

fiber optic bundle; and

b) a population of microspheres comprising at least a first and a second subpopulation, wherein each subpopulation comprises a bioactive agent and does not comprise a label, wherein said microspheres are randomly distributed on said surface.

18. A composition according to claim 1, 2, 22 or 23, wherein said substrate is selected from the group consisting of glass and plastic.

19. A composition according to claim 1, 2, 22 or 23, wherein said substrate is a fiber optic bundle.

20. A method according to claim 6, 7, 24 or 25, wherein said substrate is selected from the group consisting of glass or plastic.

21. A method according to claim 6, 7, 24 or 25 wherein said substrate is a fiber optic bundle.

22. An array composition comprising:

a) a substrate with a surface comprising discrete sites; and

b) a population of microspheres comprising at least a first and a second subpopulation, wherein said first and second subpopulations comprise:

i) a first and a second bioactive agent, respectively, wherein said bioactive agent is a protein;

ii) a first and second identifier binding ligand, respectively, wherein said identifier binding ligand is a nucleic acid; and

iii) a first and a second decoder binding ligand, bound to said first and second identifier binding ligands, respectively;

wherein said microspheres are randomly distributed on said surface.

23. An array composition comprising:

a) a substrate with a surface comprising discrete sites; and

b) a population of microspheres comprising:

i) at least a first and a second subpopulation, wherein said first and second subpopulations comprise a first and a second bioactive agent, respectively, and do not comprise a label; and

ii) a first and a second decoder binding ligand bound to said first and second bioactive agent, respectively;

wherein said microspheres are randomly distributed on said surface.

24. A method of making a composition comprising:

a) providing a surface comprising individual sites on a substrate;

b) randomly distributing microspheres on said surface such that said individual sites contain microspheres, wherein said microspheres comprise at least a first and a second subpopulation comprising a first and second bioactive agent, respectively; and

c) binding a first and second decoder binding ligand to said first and second bioactive agent, respectively;

wherein said microspheres do not comprise a label.

25. A method of making a composition comprising:

a) forming a surface comprising individual sites on a substrate;

b) randomly distributing microspheres on said surface such that said individual sites contain microspheres, wherein said microspheres comprise at least a first and a second subpopulations, wherein said first and second subpopulations comprise:

i) a first and second bioactive agent, respectively, wherein said bioactive agent is a protein; and

ii) a first and second identifier binding ligand, respectively, wherein said identifier binding ligand is a nucleic acid; and

c) binding a first and second decoder binding ligand to said first and second identifier binding ligand.

26. A method according to claim 6 further comprising:

c) binding a first and second decoder binding ligand to said first and second bioactive agent.

27. A method according to claim 7 further comprising:

c) binding a first and second decoder binding ligand to said first and second identifier binding ligand.

28. A method according to claim 24, 25, 26 or 27, wherein at least said first decoder binding ligand comprises a label.

29. A composition according to claim 3, wherein said at least one decoder binding ligand comprises a label.

30. A composition according to claim 1, wherein said first bioactive agent is said first identifier binding ligand.

31. A method according to claim 7, wherein said first bioactive agent is said first identifier binding ligand.

--32. (New) A composition according to claims 1, 4, or 22, wherein said nucleic acid is

double-stranded.

33. (New)A composition according to claim 1, 4, or 22, wherein said nucleic acid is single-stranded.

34. (New)A method according to claim 7 or 25, wherein said nucleic acid is double-stranded.

35. (New)A method according to claim 7 or 25, wherein said nucleic acid is single-stranded.

36. (New) A method according to claim 7, wherein said first and second bioactive agents are proteins.--